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(54) Title: N-(ACYLOXYMETHYL OR HYDROXYMETHYL) (OPTIONALLY (OXA OR THIA) SUBSTITUTED)BICYCLO([2.2.1] OR [2.2.2])AZALK(AN OR EN)ONE COMPOUNDS

(57) Abstract

The present invention is directed to N-(acyloxymethyl or hydroxymethyl)-(optionally (oxa or thia) substituted)bicyclo([2.2.1] or [2.2.2])azalk(an or en)one compounds which are useful as intermediates in the synthesis of cardiovascular agents, including anti-anginal agents, antihypertensives and anti-ischemics, anti-viral agents, anti-neoplastic agents, antifungal agents and antimicrobial agents, and to their preparation.

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# N-(ACYLOXYMETHYL OR HYDROXYMETHYL) (OPTIONALLY (OXA OR THIA) SUBSTITUTED)BICYCLO ([2.2.1] OR [2.2.2])AZALK(AN OR EN)ONE COMPOUNDS

## 1. Field of the Invention

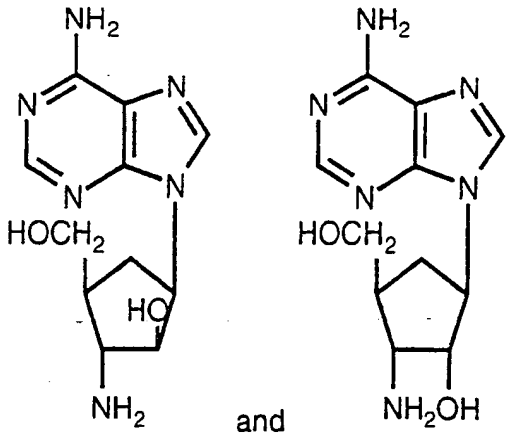
The present invention is directed to N-(acyloxymethyl or hydroxymethyl)-(optionally (oxa or thia) substituted)bicyclo([2.2.1] or [2.2.2])azalk(an or en)one compounds which are useful as intermediates in the synthesis of cardiovascular agents, including anti-anginal agents, antihypertensives and anti-ischemics, anti-viral agents, anti-neoplastic agents, antifungal agents and antimicrobial agents, and to their preparation.

### Cardiovascular Agents

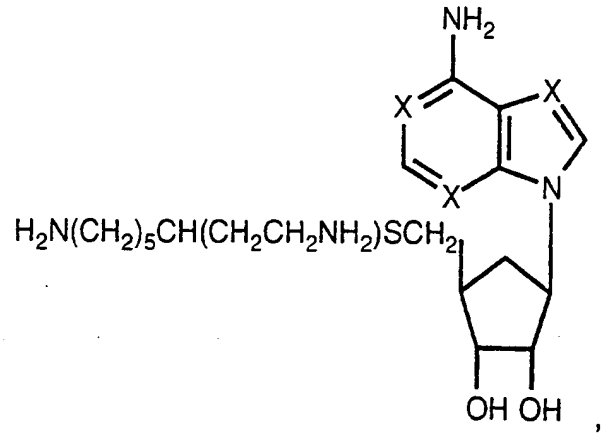
Ribose adenosine analogues having thienyl-type substituents are described in PCT WO 85/04882 (disclosing that N6-heterocyclicalkyl-substituted adenosine derivatives, including N6-[2-(2-thienyl)ethyl]amino-9-(D-ribofuranosyl)-9H-purine, exhibit cardiovascular vasodilatory activity. U.S. Pat. No. 4,954,504 and EP Publication No. 0267878 disclose carbocyclic ribose analogues of adenosine, and pharmaceutically acceptable esters thereof, substituted in the 2- and/or N6- positions by aryl lower alkyl groups including thienyl, tetrahydropyranyl, tetrahydrothiopyranyl, and bicyclic benzo fused 5- or 6- membered saturated heterocyclic lower alkyl derivatives exhibit adenosine receptor agonist properties.

### Anti-viral Agents

S. Daluge and R. Vince, J. Org. Chem., 43(12), 2311-20 (1978) disclose compounds of formulae



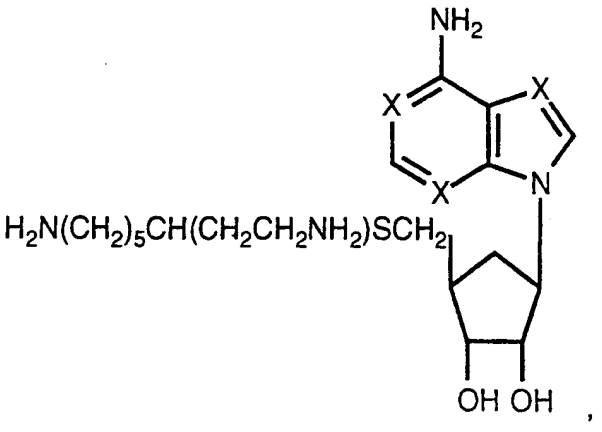

have significant antiviral activity. Carbovir, (±)-9-(cis-4-(hydroxymethyl)-2-cyclopentenyl) guanine, was disclosed as being an antiviral agent at the Second International Conference on Antiviral Research, Williamsburg, VA, April 10-14 (1988). European Patent Specification No. 349242 discloses (±)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol and (±)-cis-4-[2-amino-6-(cyclopropylmethylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol as being useful for treating HIV and HBV infections. EP Publication No. 0434450 A2 discloses that (1S,4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, (1R,4S)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, (1S,4R)-cis-4-[2-amino-6-(N-cyclopropyl-N-methylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol and (1R,4S)-cis-4-[2-amino-6-(N-cyclopropyl-N-methylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol are especially potent for treating HIV and HBV infections. United States Patent Nos. 4,383,114, 4,268,672 and 4,138,562 disclose that (±)-9-[α-(2α,3β–dihydroxy-4α-(hydroxymethyl)cyclopentyl)]-6-substituted purines are antiviral agents. United States Patent No. 4,803,272 discloses that the compound of formula




wherein X is CH or N, is useful in anti-viral therapeutic applications.

Anti-tumor Agents

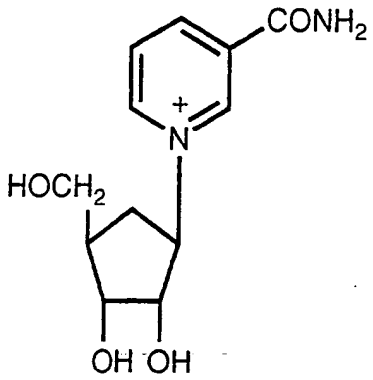
United States Patent Nos. 4,383,114, 4,268,672 and 4,138,562 disclose also that (±)-9-[α-(2α,3β–dihydroxy-4α-(hydroxymethyl)-cyclopentyl)]-6-substituted purines are anti-tumor agents. United States Patent No. 4,803,272 discloses also that the compound of formula




wherein X is CH or N, is useful in anti-tumor therapeutic applications

Anti-bacterial and antifungal Agent

M. Ikbal, et al., Eur. J. Med. Chem., 24(4), 415-20 (1989) disclose that the carbocyclic analog of nicotinamide ribose of formula

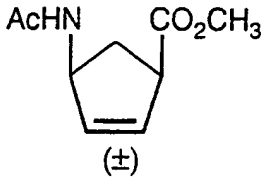


possesses good and highly specific bactericidal and fungicidal activities.

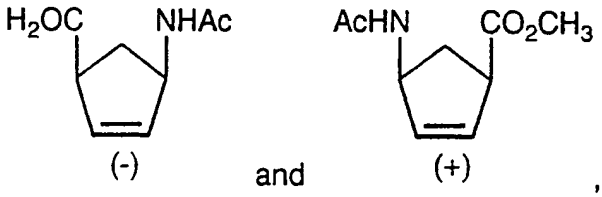
2. Recent Developments

Assorted methods are employed for preparing enantiomers of the ribose moieties and carbocyclic analogues thereof for incorporation in nucleotides and other pharmaceutically active compounds.

The biocatalytic resolution of the racemic compound of formula

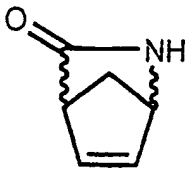


by a pig liver esterase, a hydrolase, to compounds of formulae

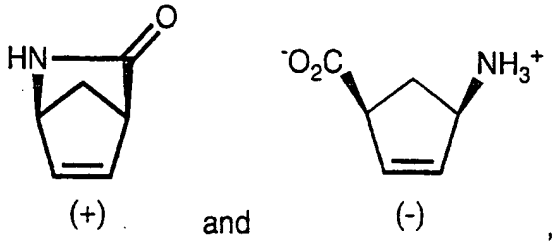


is disclosed by M. Ikbal, et al., Eur. J. Med. Chem., 24, 415 (1989). The reference does not disclose other types of enzymes for resolving methyl 4-acetamido-2-cyclopentenecarboxylic acid.

The biocatalytic resolution of a lactam, the azabicycloheptenone compound of formula

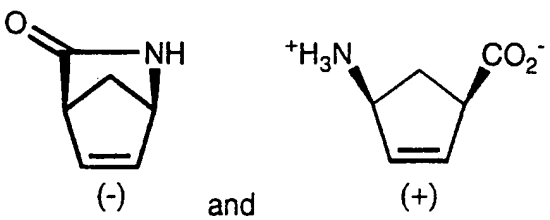


by lactamases enzymes to compounds of formulae



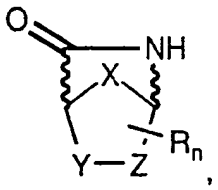
(+) and (-)

or



(-) and (+)

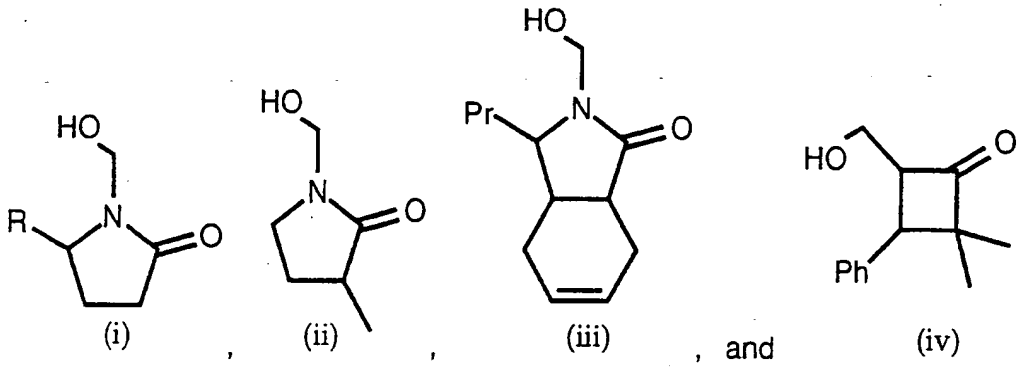
is disclosed by S. Taylor, et al., Tetrahedron: Asymmetry, 4(6), 1117 (1993); S. Taylor, et al., J. Chem. Soc. Chem. Commun., 1120 (1990) and C. Evans, et al., J. Chem. Soc., Perkin Trans. 1, 656 (1991). European Patent Application Publication No. 424,064A1 discloses racemic lactam compounds of formula



wherein X is $-CH_2-$, $-(CH_2)_2-$, -Q-, $-CH_2-Q-$ or $-Q-CH_2-$ and Q is a heteroatom (including NH); either Y and Z are independently selected from $-CH_2-$ and a heteroatom (including NH), or -Y-Z- is -CH=CH-, -CH=N- or -N=CH-; and $R_n$ is absent or represents one or more independently selected substituents at any available position(s) on the X,Y,Z-containing ring, which includes the azabicycloheptenone compound, may be resolved by lactamases. The

references do not disclose other enzymatic resolutions of the lactam compounds.

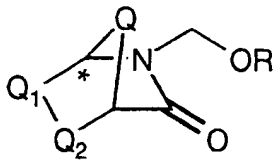
The enzymatic resolution of N-hydroxymethyl derivatives of lactam compounds of formulae




wherein R is methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl and *i*-propyl, by lipase catalyzed esterification is disclosed by B. Jonglet and G. Rousseau, Tetrahedron Letters, 34(14), 2307 (1993). H. Nagai, et al., Chem. Pharm. Bull., 40(8) 2227 (1992) also disclose the enzymatic resolution of the N-hydroxymethyl lactam compound of formula (iv) by lipase catalyzed esterification. The references do not disclose the enzymatic resolution of an N-hydroxymethyl lactam bridged bicyclo compound.

## SUMMARY OF THE INVENTION

The present invention is directed to N-(acyloxymethyl or hydroxymethyl)-(optionally (oxa or thia) substituted)bicyclo([2.2.1] or [2.2.2])azalk(an or en)one compounds of formula I



I

wherein

R is hydrogen or acyl;

Q is $Q_3$, -$Q_3$-$CH_2$-, -$CH_2$-$Q_3$-, or optionally substituted alkylene;

$Q_1$ and $Q_2$ taken together are vinylidene or optionally substituted ethylene; and

$Q_3$ is O or S,

and to methods for their preparation.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

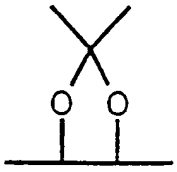
As used above, and throughout the description of this invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

The "*" symbol in the compounds according to the invention designates an optically center.

"Alkyl" means a saturated aliphatic hydrocarbon group which may be straight or branched and having about 1 to about 8 carbon atoms in the chain. Branched means that a lower alkyl group of about 1 to about 4 carbon atoms, such as methyl, ethyl, propyl or butyl is attached to a linear alkyl chain. Exemplary alkyl groups include methyl, butyl and octyl; more preferred is methyl.

"Halo substituted alkyl" means an alkyl group as defined above which is fully or partially substituted by halo groups. Exemplary halo substituted alkyl groups include carbon tetrachloride, chloroform, methylene chloride, 1,1,1-trichloroethane; more preferred is methylene chloride

"Alkylene" means a bivalent hydrocarbon chain group having from 1 to 2 carbon atoms. The alkylene group is also optionally substituted independently by one or more of alkyl, halo substituted alkyl, benzyloxy, hydroxy, halo and azido. Exemplary alkylene groups include methylene (-$CH_2$-), ethylene (-$CH_2CH_2$-), and moieties represented by the formulae

 and -CH(OH)-CH(OH)-,

which latter formula may be protected by acylation or silylation of the hydroxyl moieties therein.

"Vinylidene" means an (-CH=CH-) aliphatic hydrocarbon group.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms. Preferred monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl and cycloheptyl; more preferred is cyclopentyl. or alkyl. Exemplary multicyclic cycloalkyl rings include 1-decalin, adamant-(1- or 2-)yl and norbornyl.

"Aromatic hydrocarbon" means phenyl or naphthyl or phenyl or naphthyl substituted with one or more alkyl substituents which may be the same or different.

"Acyl" means an alkyl-CO- group. Exemplary acyl groups include acetyl, butanoyl and octanoyl; and preferred is acetyl.

"Vinyl acylate" means a group of formula $H_2C=CH-O_2C$alkyl wherein the alkyl is as defined above. Preferred vinyl acylates are include vinyl acetate and vinyl butyrate.

"Alkoxy" means an alkyl-O- group. Lower alkoxy groups are preferred. Exemplary groups include methoxy, ethoxy, n-propoxy, i-propoxy and n-butoxy.

"Benzyloxy" means phenyl-methyl-O-.

"Alcohol" means HO-alkyl or HO-cycloalkyl. Exemplary groups include methanol, ethanol, butanol, t-amyl alcohol, *i*-propanol, cyclopentanol and cyclohexanol.

"Ether" means alkyl-O-alkyl or cyclic ether where the alkyl groups are taken together to form a ring having about 3 to about 8 carbon atoms. Exemplary ethers include ethyl ether, butyl ether, isopropyl ether, *t*-butyl methyl ether, tetrahydrofuran, tetrahydropyran and dioxane.

"Ketone" means alkyl-CO-alkyl or cyclic ketone where the alkyl groups are taken together to form a ring having about 4 to about 8 carbon atoms. Exemplary ketones include acetone, pentanone, *t*-butyl methyl ketone, and cyclohexanone.

"Halide" means fluoride, chloride, bromide or iodide, and "Halo" means fluoro, chloro, bromo or iodo.

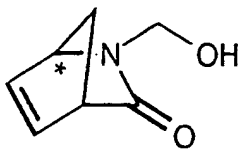
"Azido" means a group of formula -N≡N.

Description of the Preferred Embodiment

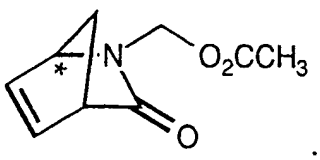
According to the compound aspect of the invention, preferred compounds are described by formula I wherein Q is optionally substituted methylene.

According to another compound aspect of the invention, preferred compounds are described by formula I wherein $Q_1$ and $Q_2$ taken together are vinylidene or substituted ethylene.

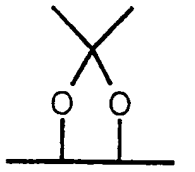
A special embodiment of the compounds according to the invention, include those of formula I wherein Q is methylene; and $Q_1$ and $Q_2$ taken together are vinylidene. Preferred species include



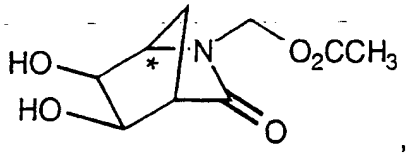
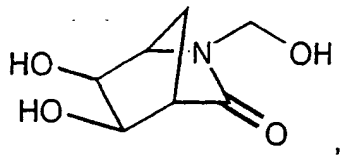

and

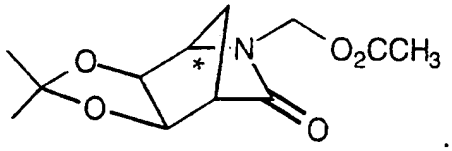



Another special embodiment of the compounds according to the invention, include those of formula I wherein Q is methylene; and $Q_1$ and $Q_2$ taken together are represented by the formula

-CH(OH)-CH(OH)- or  .

Preferred species include

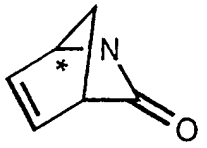
 ,  , and

 .

Another preferred aspect of compound of according to the invention is wherein the carbon designated as being an optically active by the * has the configuration (-)-(1R).

Compounds of formula I may be used by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

According to this invention compounds are useful for preparing important biological intermediates such as an enantiomer of the formula II

 II

comprising esterifying stereoselectively, by a hydrolase having such a capacity, a racemic mixture of the compound according to figure I, wherein R is hydrogen and $Q_1$ and $Q_2$ taken together are vinylidene, with a vinyl acylate in an organic solvent, whereby the esterification preferentially yields one enantiomer wherein R is acyl and $Q_1$ and $Q_2$ taken together are vinylidene and

the other enantiomer wherein R is hydrogen and $Q_1$ and $Q_2$ taken together are vinylidene.

A hydrolase for carrying out the esterification is a lipase. Particularly useful lipases are Psuedomonas lipases, such as lipase de Psuedomonas fluorescens (PS Amano), lipase de Psuedomonas fluorescens (Biocatalist), lipase de Psuedomonas fluorescens (Fluka), lipase de Psuedomonas sp. (Boehringer), lipase de Psuedomonas sp. (Sigma); more particularly lipase de Psuedomonas fluorescens (PS Amano).

A solvent for carrying out the esterification is an organic solvent selected from the group consisting of an alcohol, such as t-amyl alcohol, ether such as isopropyl ether or dioxane, ketone, such as methyl isobutyl ketone, halo substituted alkene, such as methylene chloride, and aromatic hydrocarbon, such as toluene; preferably t-amyl alcohol, isopropyl ether, methyl isobutyl ketone, methylene chloride, and toluene; and more preferably methyl isobutyl ketone and toluene.

A temperature for carrying out the esterification is from about 30°C to about 50°C; preferably at 40°C, over a time of from about 16 hours to about 40 hour.

Following the production of different enantiomers, the enantiomers, may be separated to the individual enantiomers the enantiomers; preferably by chiral HPLC chromatography. For example a Chiralcel OD column of 250 x 4.6 mm 10 μ by Diacel may be used with an eluant consisting of an organic mixture such as heptane:isopropanol (55:45) at a flow rate of about 0.5 mL/min. with U.V. detection at a 220 nm.

Following the separation of different enantiomers, the enantiomer having the acyloxymethyl moiety on the lactam nitrogen may be treated to remove the acyl moiety therefrom. That removal of the acyl moiety takes place in water or an aqueous alcohol mixture, such as methanol and water; preferably water . The removal takes place at about room temperature spontaneously.

Following the separation of different enantiomers, the enantiomer having the hydroxymethyl moiety on the lactam nitrogen may be treated to remove the hydroxymethyl moiety therefrom. That removal of the hydroxymethyl moiety from the lactam nitrogen takes place using about 2 to about 3 M ammonium hydroxide in water or an aqueous alcohol mixture, such as methanol and water; preferably in an aqueous alcohol mixture. The removal takes place at about 20°C to about 40°C, in about 1 to about 4 hours.

According to a further feature of the present invention, compounds of formula I are prepared by interconversion of other compounds of formula I.

For example, compounds of formula I wherein $Q_1$ and $Q_2$ taken together are vinylidene can be oxidized to the corresponding bishydroxylated compound of formula I or subject to halogenation across the double bond to introduce halo moieties in the compound of formula I. Compounds of formula I having halo moieties are then subject to being converted to the corresponding hydroxy, benzyloxy or azido compounds of formula I by nucleophilic displacement reactions. In addition, the compounds of formula I having hydroxy moieties therein are subject to being acylated, silylated or converted to the acetonide where the compound of formula I is bishydroxylated. According to the invention, compounds of formula I wheren R is acyl may also be prepared by acylating the corresponding compound of formula I wherein R is hydrogen with an acyl halide or acyl anhydride.

It will be apparent to those skilled in the art that certain compounds of formula I can exhibit isomerism, for example geometrical isomerism and optical isomerism. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl moieties. All isomers within formula I, and their mixtures, are within the scope of the invention.

Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

Racemic compound of formula I, wheren R is hydrogen, that is useful in undergoing the stereoselective esterification is prepared by reacting racemic compound of formula II with polyoxymethylene in the presence of a strong base, such as potassium carbonate, in an inert polar organic solvent, such as tetrahydrofuran, about reflux for about 4 hours.

The present invention is further exemplified but not limited by the following illustrative examples which illustrate the preparation of the compounds according to the invention.

Example 1

(±) N-Hydroxymethyl-2-azabicyclo [2.2.1] hept-5-en-3-one
(N-Hydroxymethyl Vince Lactam)

In a 250 mL flask, 2-azabicyclo [2.2.1] hept-5-en-3-one (Vince lactam) (5 g; 45.8 mmol), polyoxymethylene (1.4 g; 48.1 mmol), potassium carbonate (0.1 g; 0.72 mmol) and THF (50 mL) are refluxed for 4 hours. After cooling to room temperature, the light suspension is filtered, and the filtrate concentrated in vacuum to give 6.35 g (99 %) of the title product as a solid.

Example 2

(±) N-Acetoxymethyl-2-azabicyclo [2.2.1l hept-5-en-3-one

In a 25 mL flask at a temperature between 2°C and 8°C, a solution of acetyl chloride (0.35 g; 4.5 mmol) in dichloromethane (5 mL) is added dropwise to a solution of the N-hydroxymethyl Vince lactam (0.60 g; 4.3 mmol) and triethylamine (0.48 9; 4.7 mmol) in dichloromethane (5 mL). At the end of the addition, the reaction mixture is warmed to room temperature and stirred for 3 hours. After washing with brine (2 x 20 mL), drying with sodium sulfate and concentrating in vacuo, 0.67 g (86 %) of the desired compound is obtained as an oil.

In a 25 mL flask, acetic anhydride (0.86 mL; 7.78 mmol) is added dropwise at 0°C to a solution of N-hydroxymethyl Vince lactam (1.03 g; 7.41 mmol) and pyridine (0.64 mL; 8.16 mmol) in dichloromethane (8 mL). After stirring at room temperature for 6 hours, the reaction mixture is diluted with dichloromethane (7 mL), washed with brine (3 x 10 mL), dried on sodium sulfate and concentrated to give 1.22 g (92 %) of the desired compound as an oil.

Example 3

(+) N-Butyroxymethly-2-azabicyclo [2.2.1] hept-5-en-3-one

Using the same procedure as in Example 2, except using butyryl chloride instead of acetyl chloride yields the titled product (99 %).

Example 4

(-) N-Octanoyloxymethyl-2-azabicyclo [2.2.1] hept-5-en-3-one

Using the same procedure as in Example 2, except using octanoyl chloride instead of acetyl chloride yields the titled product (97 %).

Example 5

Enantioselective acetylation of N-hydroxymethyl Vince lactam using a lipase in t-amyl alcohol

In a 500 mL flask, 1.8 g of lipase PS (Amano) is added to 260 mL of t-amyl alcohol containing N-hydroxymethyl Vince lactam (2.5 g; 16.3 mmol) and vinyl acetate (2.65 mL; 28.8 mol). After incubating the mixture for 18.5 hours at room temperature, N-acetoxymethyl Vince lactam is synthesized with a 42% yield. The analysis of the reaction mixture with chiral HPLC gives the N-acetoxymethyl Vince lactam with 98% enantiomeric excess (E=100).

The reaction mixture (200 mg) is chromatographed on preparative thin layer chromatography, to separate the N-hydroxymethyl Vince lactam and N-

acetoxymethyl Vince lactam, and the acetate derivative is retrograded to the parent Vince lactam as described in the literature (Chem. Pharm Bull., 40, 2227-2229 (1992). The optical rotation of the resulting Vince lactam is negative in methanol proving that the configuration at position 1 is R.

Example 6

Enantioselective acetylation of N-hydroxymethyl Vince lactam using a lipase in toluene

In a 2 mL test tube, 10 mg of lipase PS (AMANO) are added to 1.5 mL of toluene containing N-hydroxymethyl Vince lactam (15 mg; 110 µmol) and vinyl acetate (11 µl; 120 µmol). After incubating at room temperature for 18 hours, N-acetoxymethyl Vince lactam is synthesized with a yield of 49%. The analysis of the reaction mixture with chiral HPLC gives the N-acetoxymethyl Vince lactam with more than 98% enantiomeric excess.

Example 7

Enantioselective acetylation of N-hydroxymethyl Vince lactam using a lipase in methyl isobutyl ketone

In a 2 mL test tube, 10 mg of lipase PS (AMANO) are added to 1.5 mL of methyl isobutyl ketone containing N-hydroxymethyl Vince lactam (14 mg; 100 µmol) and vinyl acetate (11 µl; 120 µmol). After incubating at room temperature for 18 hours, N-acetoxymethyl Vince lactam is synthesized with a yield of 46%. The analysis of the reaction mixture with chiral HPLC gives the N-acetoxymethyl Vince lactam with more than 98% enantiomeric excess.

Example 8

Enantioselective acylation of N-hydroxymethyl Vince lactam using a lipase in t-amyl alcohol

In a 2 mL test tube, 10 mg of lipase PS (AMANO) are added to 1.5 mL of t-amyl alcohol containing N-hydroxymethyl Vince lactam (14 mg; 100 µmol) and vinyl butyrate (120 µmol). After incubating at room temperature for 72

hours, N-butyroxymethyl Vince lactam is synthesized with a yield of 18%. The analysis of the reaction mixture with chiral HPLC gives N-butyroxymethyl Vince lactam with 96% enantiomeric excess.

Example 9

Enantioselective acetylation of N hydroxymethyl Vince lactam using a lipase in t-amyl alcohol

In a 2 mL test tube, 10 mg of lipase de *Psuedomonas fluorescens* (BIOCATALIST) are added to 1.5 mL of t-amyl alcohol containing N-hydroxymethyl Vince lactam (14 mg; 100 µmol) and vinyl butyrate (120 µmol). After incubating at room temperature for 48 hours, N-butyroxymethyl Vince lactam is synthesized with a yield of 13 %. The analysis of the reaction mixture with chiral HPLC gives N-butyroxymethyl Vince lactam with 70 % enantiomeric excess.

Example 10

Bishydroxylation of N-Acetoxymethyl Vince lactam

To a solution of N-Acetoxymethyl Vince lactam (1.73 g; 10 mmol) in t-butyl alcohol (13.3 mL) is added N-methylmorpholine N-oxide (1.29 g; 11 mmol), water (4 mL) and finally a 2.5% w/v solution of osmium tetroxide in t-butyl alcohol (0.45 mL). After stirring for 20 hours at room temperature, the reaction mixture is heated at 50°C for 20 minutes. HPLC monitoring shows that the reaction is completed, water (22 mL x 3) is added and distilled to eliminate the N-methylmorpholine, then isopropyl alcohol (22 mL x 3) is added and distilled off. The residue (2.23 g) is a mixture of N-acetoxymethyl- and N-hydroxymethyl 5,6-dihydroxy-2-azabicyclo[2.2.1]heptan-3-one as is proven by NMR.

Example 11

Formation of the acetonide

To a solution of the previous diol (2.25 g: 10.5 mmol) in acetone (9 mL) is added the 2,2-dimethoxypropane (2.25 mL) and p-toluenesulfonic acid (50 mg; 2.5% mol). After stirring for 30 minutes at room temperature, thin layer chromatography monitoring shows a complete reaction. The reaction mixture is quenched with solid sodium hydrogen carbonate. The mixture is evaporated, the residue is taken up in water and extracted with dichloromethane. After drying on sodium sulfate and evaporating to dryness, the residue (2.0 g) is extracted with cyclohexane, the black tarry residue is discarded and the clear cyclohexane solution is evaporated to dryness to give the N-methoxymethyl 5,6-dihydroxy-2-azatricyclo[2.21]heptan-3-one acetonide (1.27 g; 57%) as is demonstrated by $^1H$ NMR.

Example 12

Conversion of N-acetoxymethyl Vince lactam to Vince lactam via N-hydroxymethyl Vince lactam

In a 50 mL flask, 160 mg (880 µmole) of N-acetoxymethyl Vince lactam are added to 10 mL of water. Immediately, the N-acetoxymethyl Vince lactam is converted in N-hydroxymethyl Vince lactam. The rotary power and the composition of this solution are determined. After this analysis, we add methanol (5 mL) and 10 N ammonia (5 mL). The reaction mixture was stirred with magnetic barrel during 3.5 hours at room temperature. We obtained the Vince lactam with a yield of 80%. The vince lactam is extracted with methylene chloride and after evaporation of the solvent we add methanol. The rotary power and the composition of these two solutions are determined.

The results of these analyses are given in the following Table 1.

| Molecule | $(a)D_{25}$ | ee HPLC |
|---|---|---|
| | | |
| N-acetoxymethyl-lactam | -162 (c=0,2;MeOH) | 98% |
| | | |

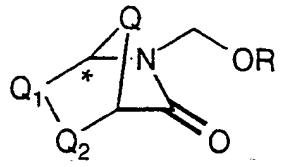
| | | |
|---|---|---|
| N-hydroxymethyl lactam | -230 (c=0,2; $H_2O$) | 98% |
| | | |
| Vince lactam | -478 (c=0,2;MeOH) - 567 (c=0,2; $CH_2Cl_2$) | 98% |

By comparison, the value published in the literature (Tetrahedron: Asymmetry, 4,6, 117-1128, 1993) for the 1R, 4S Vince lactam enantiomer is -557 (c=1; $CH_2Cl_2$).

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

WHAT IS CLAIMED IS:

1. A compound of formula I



I

wherein

R is hydrogen or acyl;

Q is $Q_3$, $-Q_3-CH_2-$, $-CH_2-Q_3-$, or optionally substituted alkylene;

$Q_1$ and $Q_2$ taken together are vinylidene or optionally substituted ethylene; and

$Q_3$ is O or S.

2. The compound of claim 1 wherein

Q is optionally substituted methylene.

3. The compound of claim 1 wherein

$Q_1$ and $Q_2$ taken together are vinylidene or substituted ethylene.

4. The compound of claim 1 wherein

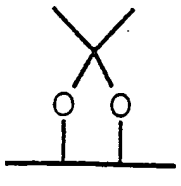
Q is methylene; and

$Q_1$ and $Q_2$ taken together are vinylidene.

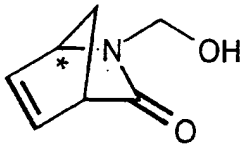
5. The compound of claim 1 wherein

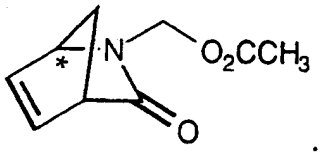
Q is methylene; and

$Q_1$ and $Q_2$ taken together are represented by the formula

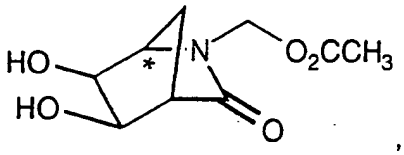
-CH(OH)-CH(OH)- or  .

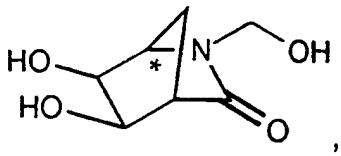
6. The compound of claim 1 which is

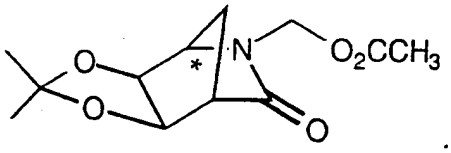


or



7. The compound of claim 1 which is

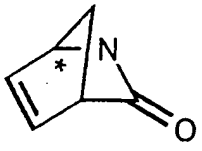


,


, or



8. The compound of according to claim 1 wherein the carbon designated as being an optically active by the * has the configuration (-)-(1R).

9. A process for preparing an enantiomer of the formula II



II

comprising esterifying stereoselectively, by a hydrolase having such a capacity, a racemic mixture of the compound according to claim 1 wherein R is hydrogen with a vinyl acylate in an organic solvent, whereby the esterification

preferentially yields one enantiomer wherein R is acyl and the other enantiomer wherein R is hydrogen.

10. The process of claim 9, wherein the hydrolase is a lipase.

11. The process of claim 10, wherein the lipase is a Psuedomonas lipase.

12. The process of claim 11, wherein the Psuedomonas lipase is lipase PS.

13. The process of claim 9, wherein the organic solvent is selected from the group consisting of an alcohol, ether, ketone, halogenated alkyl, and aromatic hydrocarbon.

14. The process of claim 13, wherein the organic solvent is selected from the group consisting of t-amyl alcohol, isopropyl ether, methyl isobutyl ketone, methylene chloride, and toluene.

15. The process of claim 14, wherein the organic solvent is selected from the group consisting of methyl isobutyl ketone and toluene.

16. The process of claim 9, wherein the esterifying takes place from about 20°C to about 50°C.

17. The process of claim 16, wherein the esterifying takes place at about 25°C.

18. The process according to claim 9, further comprising separating the enantiomers.

19. The process according to claim 18, wherein the separating is by chiral HPLC.

20. The process according to claim 9, further comprising removing the acyl moiety from the acyloxymethyl moiety on the lactam nitrogen in the enantiomer.

21. The process according to claim 20, wherein the removal of the acyloxy moiety takes place in water or an aqueous alcohol mixture.

22. The process according to claim 9, further comprising removing hydroxymethyl from the lactam nitrogen moiety in the enantiomer.

23. The process according to claim 22, wherein the removal of the hydroxymethyl from the lactam nitrogen moiety takes place with ammonium hydroxide in an aqueous alcohol mixture.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/11579

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :544/47, 92, 105; 546/114, 116, 183

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/47, 92, 105; 546/114, 116, 183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>--<br>Y | TETRAHEDRON:ASYMMETRY, Volume 5, Number 7, issued 1994, Nakano et al, "A Facile Lipase-Catalyzed Resolution of 2-Azabicyclo[2.2.1]hept-5-en-3-ones", pages 1155-1156, see page 1156. | 1-4, 6, 8, 9-23<br>----------<br>1-4, 6, 8, 9-23 |
| Y | US, A, 5,248,610 (MIYAZAWA ET AL.) 28 September 1993, see column 4, lines 28-34 and column 8, Examples 2, 3. | 9-23 |
| A | US, A, 5,284,769 (EVANS et al.) 08 February 1994, see columns 1-3. | 1-23 |
| A | CHEMICAL PHARMACEUTICAL BULLETIN, Volume 39, Number 5, Katagiri et al., issued May 1991, pages 1112-1122, see page 1113, chart 3. | 1-8 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>20 SEPTEMBER 1996 | Date of mailing of the international search report<br>29 OCT 1996 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>IW for<br>EVELYN HUANG<br>Telephone No. (703) 308-1235 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/11579

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 221/02, 265/04, 265/28, 279/04, 279/10, 471/08, 491/056